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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/459,808      | 12/13/1999  | AVI J. ASHKENAZI     | P0978-1C1           | 1650             |

7590 05/14/2004

ATTN DIANE L MARSCHANG  
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EXAMINER

ROMEO, DAVID S

ART UNIT PAPER NUMBER

1647

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                                      |  |  |
|------------------------------|--------------------------------------|--|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>09/459,808 | <b>Applicant(s)</b><br>ASHKENAZI, AVI J. |  |
|                              | <b>Examiner</b><br>David S Romeo     | <b>Art Unit</b><br>1647                  |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 February 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 69-87 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 80-87 is/are allowed.
- 6) ☒ Claim(s) 69-73, 75, 77 and 78 is/are rejected.
- 7) ☒ Claim(s) 74, 76 and 79 is/are objected to.
- 8) ☒ Claim(s) 69-87 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>200402</u> . | 6) <input type="checkbox"/> Other: _____  |

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**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Claims 69-87 are pending and being examined to the extent that they read upon the elected species 5-FU and polyethylene glycol.

***Claim Rejections - 35 USC § 103***

Claims 69, 77, 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiley (25, cited by Applicants). This rejection is based upon an effective filing date of June 29, 1995 for Wiley. Wiley teaches a soluble TRAIL ligand, which is a fragment of a polypeptide comprising amino acid residues 114-281 of SEQ ID NO: 1 as recited in the present claims, as indicated below:

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CC Sequence 2, Application US/08670354
CC Patent No. 5763223
CC GENERAL INFORMATION:
CC APPLICANT: Steven R. Wiley and
CC INFORMATION FOR SEQ ID NO: 2:
CC SEQUENCE CHARACTERISTICS:
CC LENGTH: 281 amino acids
CC TYPE: amino acid
CC TOPOLOGY: linear
CC MOLECULE TYPE: protein
SQ SEQUENCE 281 AA; 32509 MW; 420741 CN;

Query Match 100.0%; Score 1227; DB 2; Length 281;
Best Local Similarity 100.0%; Pred. No. 7.88e-109;
Matches 168; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Db 114 VRERGPQRVAAHITGTRGRSNTLSSPNSKNEKALGRKINSWESSRSGHSFLSNLHLRNGE 173
QY 114 VRERGPQRVAAHITGTRGRSNTLSSPNSKNEKALGRKINSWESSRSGHSFLSNLHLRNGE 173

Db 174 LVIHEKGFYIYSQTYFRFQEEIKENTKNDKQMVQYIYKYTSYPDPILLMKSARNSCWSK 233
QY 174 LVIHEKGFYIYSQTYFRFQEEIKENTKNDKQMVQYIYKYTSYPDPILLMKSARNSCWSK 233

Db 234 DAEVGLYSIYQGGIFELKENDRIFVSVTNEHLIDMDHEASFFGAFIVG 281
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|||||  
QY 234 DA EYGLYSIQGGIFELKENDRI FVSVTNEHLIDMDHEASFFGAPLVG 281,

fragments of the extracellular domain that retain a desired biological activity (paragraph bridging  
5 columns 4-5), and expression of TRAIL polypeptides in bacterial expression systems, such as E.  
coli, which provides non-glycosylated molecules (column 8, last full paragraph). Wiley is  
evidence that it is routine to characterize proteins in terms of the minimum size required for  
activity. Accordingly, it would have been obvious to one of ordinary skill in the art at the time  
of Applicants' invention to make a fragment of a polypeptide comprising or consisting of amino  
10 acid residues 114-281 of SEQ ID NO: 1, with a reasonable expectation of success. One of  
ordinary skill in the art would be motivated to make this modification in order to obtain a  
fragments of the extracellular domain that retains a desired biological activity, namely,  
apoptosis. Wiley also teaches that TRAIL polypeptides may be employed in treating cancer,  
including leukemia, lymphoma, and melanoma (column 18, full paragraph 1). TRAIL may be  
15 administered in conjunction with other agents that exert a cytotoxic effect on cancer cells  
(column 18, full paragraph 3). Wiley is silent with respect to the treatment of blastoma.  
However, a blastoma is a type of cancer. See the present specification at page 12, full paragraph  
1, of the present specification. The examiner uses the present specification as dictionary for a  
definition of the term "blastoma". It would have been obvious to one of ordinary skill in the art  
20 at the time of Applicants' invention to treat cancer, including leukemia, lymphoma, and  
melanoma, with soluble TRAIL polypeptides and fragments thereof, as taught by Wiley, and to  
modify that teaching by treating blastoma, with a reasonable expectation of success. One of  
ordinary skill in the art would be motivated to make that modification in order to induce

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apoptosis in the blastoma cells and treat the blastoma. The invention is prima facie obvious over the prior art.

Claims 69, 70-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiley

5 (25, cited by Applicants) as applied to claim 69 above, and further in view of Gmeiner (A).

Wiley teaches that TRAIL polypeptides may be employed in treating cancer, including leukemia, lymphoma, and melanoma (column 18, full paragraph 1) and that TRAIL may be administered in conjunction with other agents that exert a cytotoxic effect on cancer cells (column 18, full paragraph 3), as discussed above. Wiley is silent with respect to administering

10 TRAIL in conjunction with 5-FU.

Gmeiner discloses that 5-FU exerts a cytotoxic effect on cancer cells (column 4, line 41). Gmeiner does not teach TRAIL.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to employ TRAIL in treating cancer and administer TRAIL in conjunction  
15 with other agents that exert a cytotoxic effect on cancer cells, as taught by Wiley, and to modify that teaching by administering TRAIL and 5-FU with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because 5-FU exerts a cytotoxic effect on cancer cells. Furthermore, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by  
20 routine experimentation. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer TRAIL and 5-FU either concurrently or sequentially. The invention is prima facie obvious over the prior art.

Claims 69, 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiley (25, cited by Applicants) as applied to claim 69 above, and further in view of Davis (e15).

Wiley teaches the treatment of cancer with TRAIL, as discussed above. Wiley does not  
5 teach TRAIL linked to PEG.

Davis discloses that coupling of polypeptides to polyethylene glycol to provides a physiologically active non-immunogenic water soluble polypeptide composition. The polyethylene glycol protects the polypeptide from loss of activity and the composition can be injected into the mammalian circulatory system with substantially no immunogenic response.  
10 See the Abstract. Davis does not teach treatment of cancer with TRAIL.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat cancer with TRAIL, as taught by Wiley, and to modify that teaching by linking TRAIL to PEG, as taught by Davis, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to provide  
15 a physiologically active non-immunogenic water soluble TRAIL composition, protected from loss of activity and that can be injected into the mammalian circulatory system with substantially no immunogenic response. The invention is prima facie obvious over the prior art.

### ***Conclusion***

20 Claims 80-87 are allowable. Claims 74, 76, and 79 are objected to.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (571) 272-0887.

25 IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHT FAX NUMBERS:

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BEFORE FINAL (703) 872-9306

AFTER FINAL (703) 872-9307

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.



DAVID ROMEO  
PRIMARY EXAMINER  
ART UNIT 1647

DSR  
MAY 13, 2004